Crusted Papules in a Linear Distribution on the Leg of an Adult Woman

Jason Emer, MD; Kristen Pacific; Brian Marciniak, BS; Harleen Sidhu, MD; Robert Phelps, MD

Case Report

A 66-year-old Caucasian woman with a past medical history of fibromyalgia and hypothyroidism presented to the outpatient dermatology clinic with a 27-year history of skin lesions on the back of her left leg. The skin lesions started as a few "small bumps" that enlarged and spread over years down her entire left leg. The patient reported rare spontaneous improvement, but frequent flares with extreme pruritus. Previous physicians had diagnosed eczema and prescribed topical corticosteroids without any improvement. Review of systems was negative. Upon examination, there were multiple keratotic and crusted papules, varying in color from yellow to red-brown, clustered in a linear or segmental arrangement down the left posterior leg (Figures 1a and 1b). There was no nail or mucous membrane involvement. A punch biopsy was performed on the left posterior thigh (Figure 2a–2c).

Diagnosis

Linear Darier's disease (DD)

Microscopic Findings and Clinical Course

Histopathological examination revealed scattered foci of suprabasal acantholysis within spongiotic foci and dyskeratotic cells in the epidermis (Figures 2a–2b). The dermis contained a perivascular mononuclear infiltrate. Corps ronds and grains were demonstrated in the superficial epidermis (Figure 2c). The histopathological findings of focal acantholytic dyskeratosis and spongiosis with the above clinical findings were consistent with a diagnosis of DD.

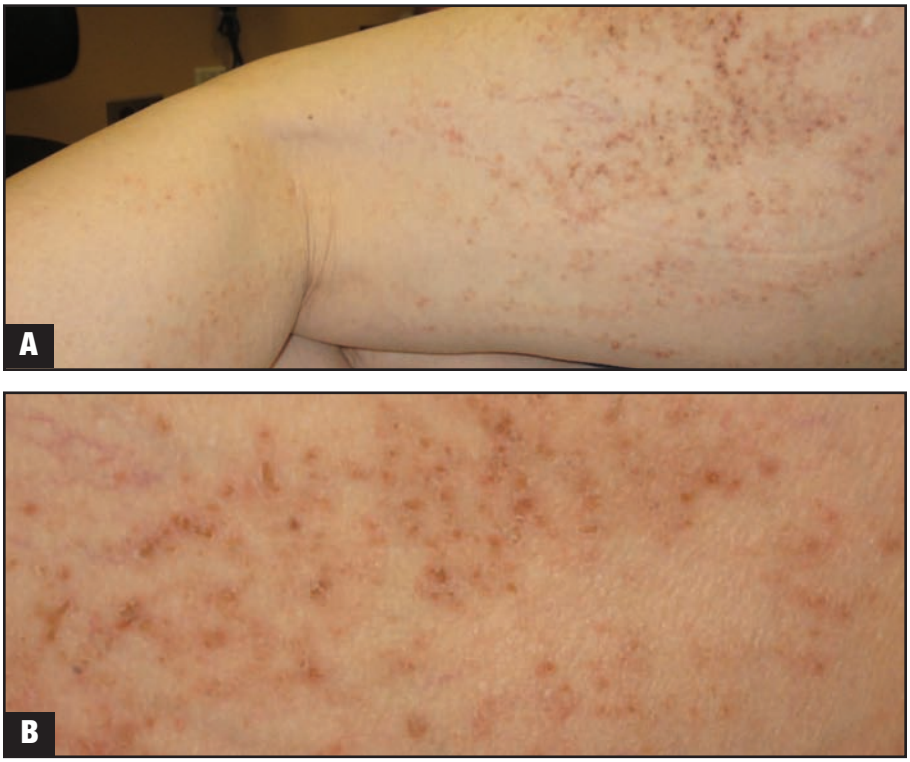
Discussion

First described in 1889, DD (also known as keratosis follucularis or Darier-White disease) is an uncommon autosomal-dominant genodermatosis.[1,2] Located on chromosome 12q23-24.1 is ATP2A2, the gene responsible for encoding sarco- and endoplasmic reticulum calcium (Ca2+)-adenosine triphosphate (ATP) isoform 2 protein (SERCA2).[1-3] Mutations of the ATP2A2 gene have been identified as the cause and gene sequencing can confirm the diagnosis.[4,5] Alterations in Ca2+ regulation may affect the synthesis, folding, or trafficking of desmosomal proteins, such as desmoplakins.[6,7] Further, Ca2+ dysregulation may lead to impaired control of cell cycle checkpoints, leading to increased epidermal sensitivity to skin trauma and subsequent keratinocyte apoptosis.[8]

Classic lesions are described as skin-colored, red, or yellow-brown crusted papules with a greasy or warty texture distributed in seborrheic regions, such as the nasolabial folds, ears, chest, and back (Figure 3).[2,3,9] Flexural involvement is common and often associated with malodor, which can cause psychological disturbance.[10] Warty, flat-topped papules or plaques on the hands are referred to as acrokeratosis verruciformis of Hopf, which is more commonly seen as a localized form (Figure 4). Onset is typically before the third decade of life and may be associated with severe pruritus. Heat, sweat, humidity, sunlight, ultraviolet B, lithium, oral corticosteroids, mechanical trauma, neuropsychiatric disorders, and menstruation have all been reported to cause disease exacerbation.[11,12]

Other clinical characteristics include palmar or nail changes including punctate keratoses or pits, subungual hyperkeratosis, fragile, brittle nails with red and white longitudinal bands, and/or triangular nicks in the distal nail plate frequently termed "V-shaped nicking"(Figures 5a–5b).[3] Mucous membrane involvement often shows white papules with central depression referred to as "cobblestoning" and can appear in the mouth or anogenital areas.

Histotopathology shows acantholysis with dyskeratosis and the formation of corps ronds and grains.[2,3] Acantholysis frequently causes the formation of suprabasalar clefts and the underlying dermal papilla project into these clefts covered by a single layer of basilar epithelium (stratum basale) forming villus-like structures. Hykerkeratosis is common as well as a large keratin plug showing focal parakeratosis overlying each lesion. Corps ronds and grains represent dyskeratotic cells, the former being



Figures 1A and 1B. Clinical photograph. Keratotic crusted papules clustered in a linear distribution down the posterior left thigh—A) far; B) up close

located in the stratum spinosum or granulosum and characterized by an irregular eccentric and sometimes pyknotic nucleus, a clear perinuclear halo, and a brightly eosinophilic cytoplasm; the latter located in the stratum corneum and consisting of oval cells with elongated cigar-shaped nuclei and abundant keratohyalin granules.

Approximately 10 percent of DD cases present in a localized pattern, a likely result of genetic mosaicism in the ATP2A2 gene.[1–3,9] Other names, such as linear, unilateral, segmental, or zosteriform DD, have been described in the literature and represent the classic clinical lesions in localized aggregates. This disease variant occurs with equal frequency in men and women.[13]

Although histologically identical to classical DD, the linear variant was first differentiated in 1906 and unlike the generalized form, the linear variant presents with a negative family history and lacks nail, mucosal, and palmoplantar abnormalities, as was demonstrated in the patient described in this case.[1–3,13] The differential diagnoses include eczema, dermatitis herpetiformis, Grover's disease, inflammatory linear verrucous epidermal nevus (ILVEN), linear psoriasis, linear lichen planus, linear Hailey-Hailey, and verrucous epidermal nevi.[1,5]

Linear DD has two subclassifications. The more common of the two subtypes is type 1, which presents unilaterally along Blaschko's lines. Type 2 consists of linear streaks and is a more severe, rare form of the disease.[1–3] Both types occur as a result of genetic mosaicism: type 1, from postzygotic somatic mutations, and type 2 from a heterozygous germline mutation including somatic loss of heterozygosity of the wild-type allele in a segmental area.[2,14] Because mutations of germline cells (unlike those of somatic cells) are heritable, patients with type 2 linear DD may have offspring with the generalized form of the disease.[15]

Treatment is difficult and focused on reducing hyperkeratosis to flatten or clear the papules. Current management includes limiting exposure to aggravating factors and offering topical, systemic, surgical, and/or laser therapies depending on disease severity. To prevent exacerbation, patients should wear daily sunscreen and breathable or moisture-wicking clothing and limit exposure to heat, humidity, and sunlight. Topical corticosteroids reduce inflammation and cause epidermal atrophy, antiseptics (e.g., dial, hibiclens) and bleach baths decrease bacterial colonization and proliferation, and keratolytics (e.g., urea, salicyclic acid), and barrier repair moisturizers help reduce hyperkeratosis.[7,13] Other treatments include the use of topical (e.g., tazarotene or tretinoin) or oral (e.g., isotretinoin or acitretin) retinoids, which may also regulate the hyperkeratosis and reduce flares. Systemic therapies including the use of oral antibiotics and/or oral antivirals (e.g., acyclovir, valacyclovir) may be needed for the treatment of cutaneous infections or used as a preventative measure during episodic flares.[10,14] Dermabrasion, electrosurgery, Mohs surgery, excision, lasers (e.g., carbon dioxide (CO_2), erbium-doped yttrium aluminium garnet (Er:YAG), pulsed dye), and photodynamic therapy are surgical options demonstrating variable results in the literature.[1,14,16] Additionally, botulinum toxin type A

injections have been shown to reduce pain and discomfort, likely a consequence of sweat reduction limiting disease exacerbation.[17] Thus, topical (e.g., aluminum chloride solution) and/or oral medications (e.g., glycopyrrolate, clonidine, clonazepam) used for the treatment of hyperhidrosis should be accompanying treatment agents. Sweat reduction may help in reducing disease flares as well as treatment of the associated foul odor. Lastly, genetic counseling for those planning to have children and psychiatric referral for those with emotional distress should be sought.

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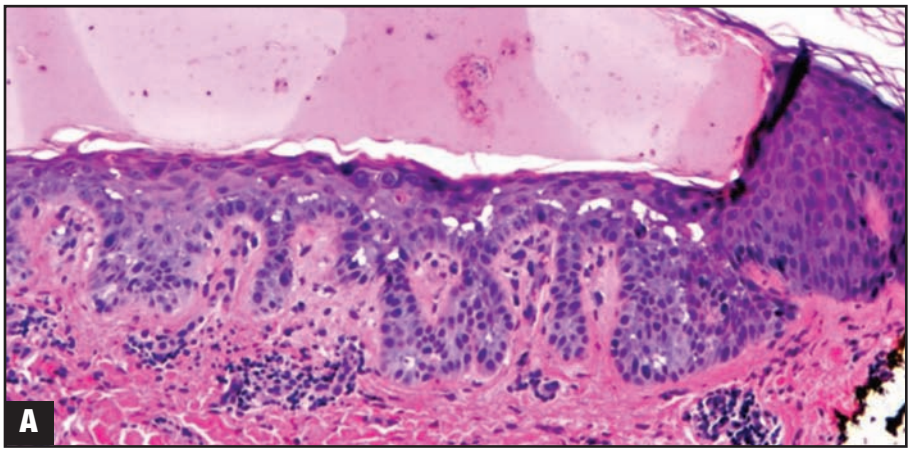
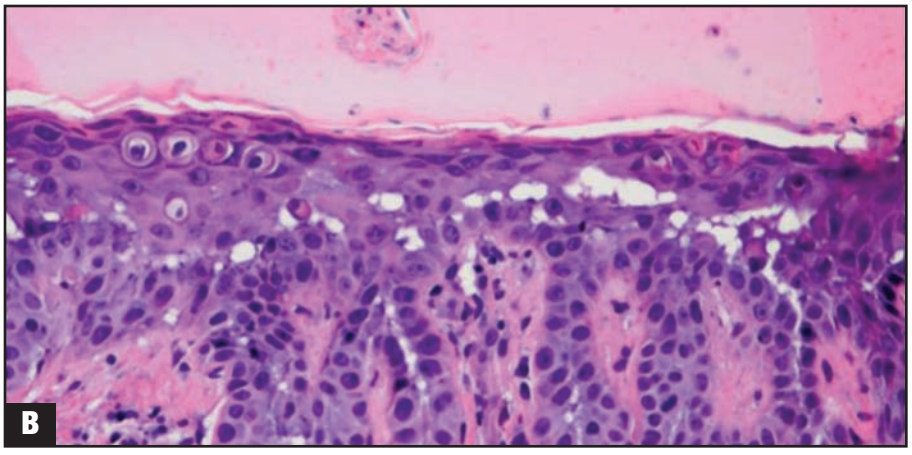
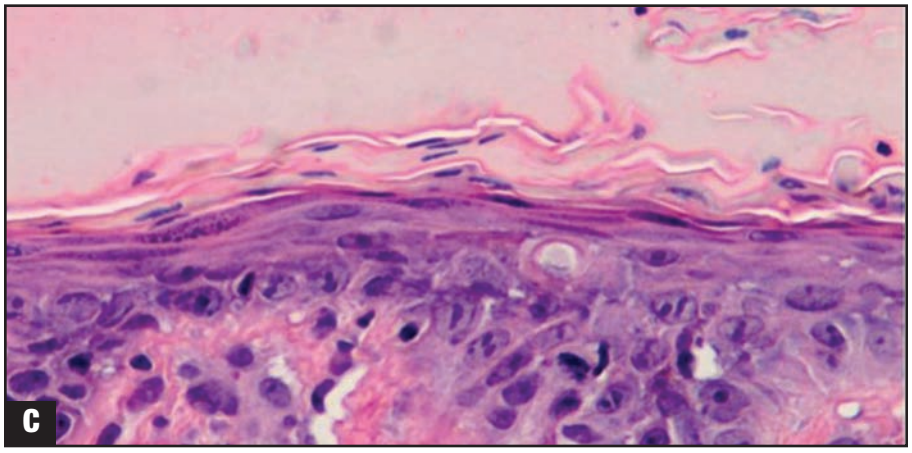






Figures 2A–2C. Histopathology. A) Suprabasal cleft with focal acantholytic dyskeratosis and spongiosis (H&E, 40X). B and C) On higher magnification, dyskeratotic cells are appreciated (H&E, 100X and 400X)

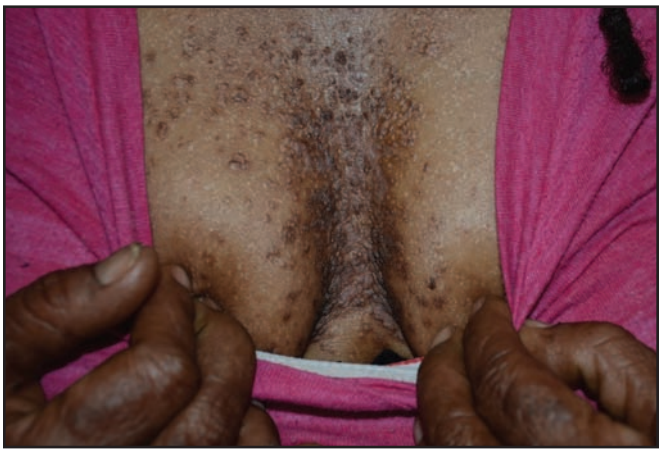


Figure 3. Verrucous, greasy-appearing, red-brown papules concentrated on the central chest (seborrheic distribution) in a patient with classic DD

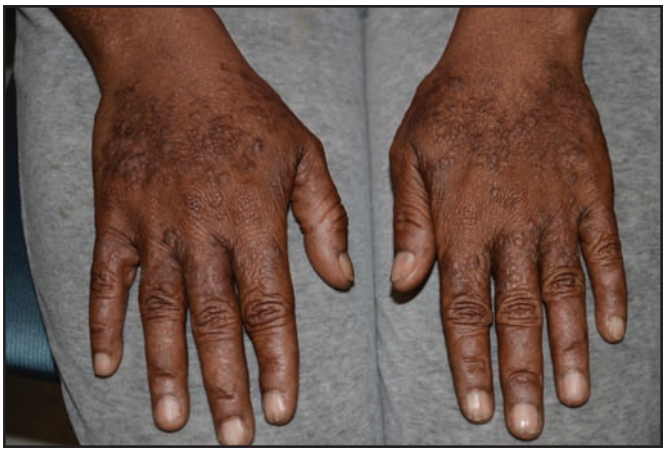
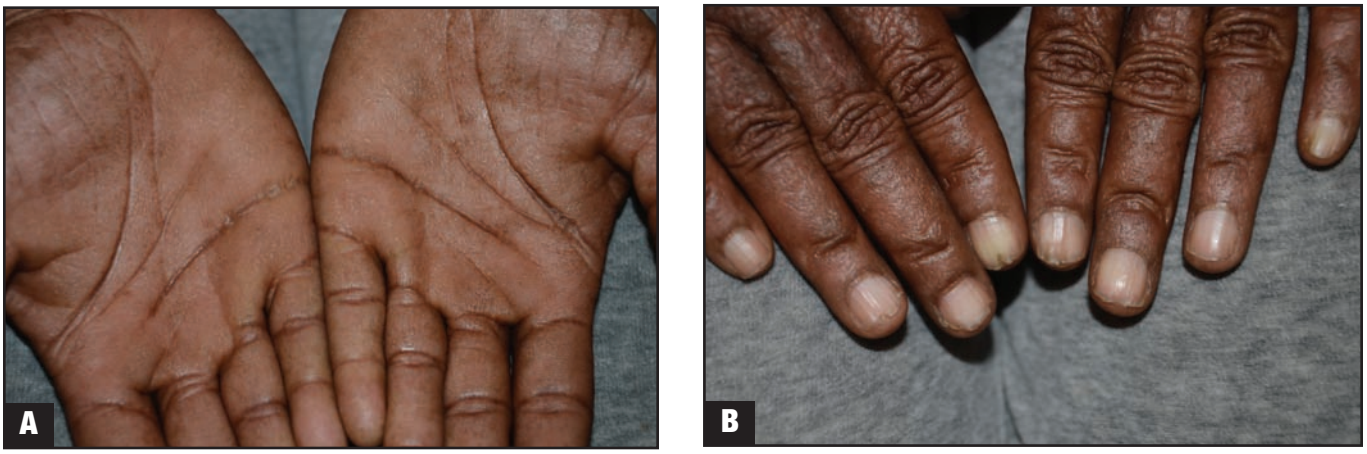


Figure 4. Acrokeratosis verruciformis of Hopf. Verroucous papules and plaques on the dorsal hands



Figures 5A and 5B. Associated findings. A) Palmar pits; B) Red and white longitudinal bands with distal V-shaped nicking of all nails

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Dr. Emer and Mr. Marciniak are from Mount Sinai School of Medicine, Department of Dermatology, New York, New York. Ms. Pacific is from Dickinson College, Carlisle, Pennsylvania. Disclosure: The authors report no relevant conflicts of interest. Address correspondence to: Jason Emer, MD, Mount Sinai School of Medicine, Department of Dermatology, 5 East 98th Street, 5th Floor, New York, New York 10029; E-mail: Jason.emermd@gmail.com

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